#6

DOCKET NO. JAB1703USPCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Anne Simone Josephine Lesage et al.

Serial No.: 10/509,069 Art Unit:

I.A. Filing Date: March 26, 2003 Examiner:

For : RADIOLABELLED QUINOLINE AND QUINOLINONE DERIVATIVES AND THEIR USE AS METABOTROPIC GLUTAMATE RECEPTOR LIGANDS

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

November 18, 2005

(Date of Deposit)

Hal B. Woodrow

(Name of applicant, assignee, or Registered Representative)

/Hal Brent Woodrow, Reg.# 32,501/

(Signature)

November 18, 2005

(Date of Signature)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTIFICATION TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Dear Sir:

Applicant's attorney is in receipt of the Notification To Comply With Requirements For Patent Applications Containing Nucelotide And/Or Amino Acid Sequence Disclosures.

With respect to defects in the previously submitted Preliminary Amendment, applicant has now corrected said defects and now submits a revised Preliminary Amendment for entry.

With respect to the requirement for submission of a sequence listing, applicant's attorney has reviewed the above-identified patent

application and has not found any nucleic acid or amino acid sequences that would require a sequence listing.

The abbreviations on page 108 of the specification are for compounds only. For the Examiner's convenience, applicant is attaching copies of webpages from the Tocris Bioscience website and the Perkin Elmer website listing the full names of the compounds listed on page 108 of the specification.

Accordingly, applicant's attorney respectfully requests withdrawal of the requirement to provide a sequence listing for this application.

In addition, applicant does not believe that any extension fees or other patent fees are due at this time since the Notification to Comply was issued in error. If, however, the Patent Office does deem any fee necessary at this time, the Commissioner is then hereby authorized to charge said required fee to Deposit Account No. 10-0750/JAB1703USPCT/HBW. This sheet is submitted in triplicate.

Respectfully submitted,

/Hal Brent Woodrow/
Hal B. Woodrow
Reg. No. 32,501
Attorney for Applicant(s)

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-2976

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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/509,069	Anne Simone Josephine Lesage	JAB-1703

INTERNATIONAL APPLICATION NO.	
PCT/EP03/03240	
I.A. FILING DATE	PRIORITY DATE
03/26/2003	03/29/2002

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CONFIRMATION NO. 3249

371 FORMALITIES LETTER

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Date Mailed: 06/24/2005

NOTIFICATION TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to file the items indicated below to avoid abandonment. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

- This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c) Applicant must provide an initial paper or compact disc copy of the "Sequence Listing", as well as an amendment directing its entry into the application and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000).
- A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If applicant desires the sequence listing in the instant application to be identical with that of another application on file in the U.S. Patent and Trademark Office, such request in accordance with 37 CFR 1.821(e) may be submitted in lieu of a new CRF.

Additionally the following defects have been observed:

- Preliminary Amendments have not been entered because Original application consists of claims 1-20. Preliminary Amendment addresses only claims 1-17. Please clarify the status of claims 18-20..

For questions regarding compliance to 37 CFR 1.821-1.825 requirements, please contact:

- **For Rules Interpretation, call (571) 272-0951**
- **For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.**

- **Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov**

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

*A copy of this notice **MUST** be returned with the response.*

BARBARA A CAMPBELL

Telephone: (703) 308-9140 EXT 217

PART 1 - ATTORNEY/APPLICANT COPY

U.S. APPLICATION NUMBER NO.	INTERNATIONAL APPLICATION NO.	ATTY. DOCKET NO.
10/509,069	PCT/EP03/03240	JAB-1703

FORM PCT/DO/EO/922 (371 Formalities Notice)

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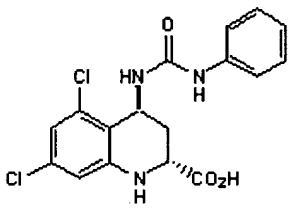
0742 L-689,560



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Biological Activity:

Very potent antagonist at the glycine-NMDA site.

References:

Leeson *et al (1991) trans-2-Carboxy-4-substituted tetrahydroquinolines. Potent glycine-site NMDA receptor antagonists. Med.Chem.Res.* ***1*** *64.* ***Leeson*** *et al (1992) 4-Amido-2-carboxytetrahydroquinolines. Structure-activity relationship for antagonism at the glycine site of the NMDA receptor. J.Med.Chem.* ***35*** *1954.* ***Stone*** *(2000) Development and therapeutic potential of kynurenic acid and kynurenine derivatives for neuroprotection. TiPS* ***21*** *149.*

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10 mg / $109.00 0

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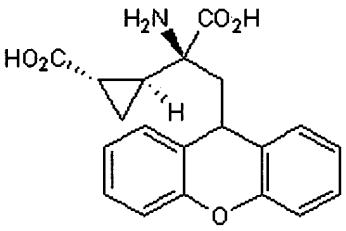

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Biological Activity:

Highly potent and selective group II metabotropic glutamate receptor antagonist (K_i/IC_{50} values are 2.3, 1.3, 173, 990, 6800, 8200 and 22000 nM for human $mGlu_2$, $mGlu_3$, $mGlu_8$, $mGlu_7$, $mGlu_1$, $mGlu_5$ and $mGlu_4$ receptors respectively). Readily brain penetrant and active in vivo.

References:

Ornstein *et al (1998) 2-Substituted (2SR)-2-amino-2-((1SR,2SR)-2-carboxycycloprop-1-yl) glycines as potent and selective antagonists of group II metabotropic glutamate receptors. 2. Effects of aromatic substitution, pharmacological characterization, and bioavailability. J.Med.Chem.* ***41*** *358.* ***Kingston*** *et al (1998) LY341495 is a nanomolar potent and selective antagonist of group II metabotropic glutamate receptors. Neuropharmacology* ***37*** *1.* ***Fitzjohn*** *et al (1998) The potent mGlu receptor antagonist LY341495 identifies roles for both cloned and novel mGlu receptors in hippocampal synaptic plasticity. Neuropharmacology* ***37*** *1445.* ***Johnson*** *et al (1999) [^{3}H]-LY341495 as a novel antagonist radioligand for group II metabotropic glutamate receptors: characterization of binding to membranes of mGlu receptor subtype expressing cells. Neuropharmacology* ***38*** *1519.*

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Price:

10 mg / $325.00 0

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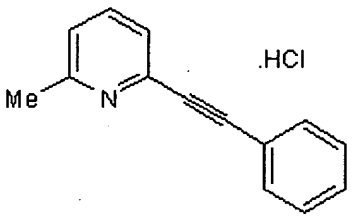
1212 MPEP hydrochloride



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Biological Activity:

Potent and highly selective non-competitive antagonist at the $mGlu_5$ receptor subtype (IC_{50} = 36 nM). Centrally active following systemic administration in vivo.

References:

***Bowes** et al (1999) Anti-hyperalgesic effects of the novel metabotropic glutamate receptor 5 antagonist, methylphenylethynylpyridine, in rat models of inflammatory pain. Br.J.Pharmacol. **126** 250P. **Salt** et al (1999) Antagonism of the mGlu5 agonist 2-chloro-5-hydroxyphenylglycine by the novel selective mGlu5 antagonist 6-methyl-2-(phenylethynyl)-pyridine (MPEP) in the thalamus. Br.J.Pharmacol. **127** 1057. **Gasparini** et al (1999) 2-Methyl-6-(phenylethynyl)-pyridine (MPEP), a potent, selective and systemically active mGlu5 receptor antagonist. Neuropharmacology **38** 1493. **Malherbe** et al (2003) Mutational analysis and molecular modeling of the binding pocket of the metabotropic glutamate 5 receptor negative modulator 2-methyl-6-(phenylethynyl)-pyridine. Mol.Pharmacol. **64** 823.*

Price:

10 mg / $89.00 0

50 mg / $395.00 0

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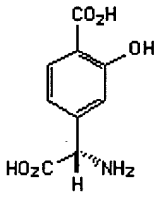
0320 (S)-4-Carboxy-3-hydroxyphenylglycine

Alternative name(s):

(S)-4C3HPG



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Biological Activity:

Competitive antagonist at group I $mGlu_{1a/1a}$ receptors, mixed effect at $mGlu_{5a/5b}$ receptors; agonist at group II metabotropic glutamate receptors.

References:

Birse *et al (1993) Phenylglycine derivatives as new pharmacological tools for investigating the role of metabotropic glutamate receptors in the central nervous system. Neuroscience **52** 481.* ***Hayashi*** *et al (1994) Analysis of agonist and antagonist activities of phenylglycine derivatives for different cloned metabotropic glutamate receptor subtypes. J.Neurosci. **14** 3370.* ***Kingston*** *et al (1995) Pharmacological analysis of 4-carboxyphenylglycine derivatives: comparison of effects mGluR1α and mGluR5a subtypes. Neuropharmacology **34** 887.* ***Sekiyama*** *et al (1996) Structure-activity relationships of new agonists and antagonists of different metabotropic glutamate receptor subtypes. Br.J.Pharmacol. **117** 1493.*

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0284 (1S,3*R*)-ACPD

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Biological Activity:

Active isomer of (±)-trans-ACPD. Active at both group I and II mGlu receptors.

References:

Irving *et al (1990) 1S,3R-ACPD stimulates and L-AP3 blocks* Ca^{2+} *mobilization in rat cerebellar neurons. Eur.J.Pharmacol.* ***186*** *363.* ***Pin and Duvoisin*** *(1995) The metabotropic glutamate receptors: structure and functions. Neuropharmacology* ***34*** *1.* ***Knopfel*** *et al (1995) Metabotropic glutamate receptors: novel targets for drug development. J.Med.Chem.* ***38*** *1417.* ***Mistry and Challiss*** *(1996) Differences in agonist and antagonist activities for two indicies of metabotropic glutamate receptor-stimulated phosphoinositide turnover. Br.J.Pharmacol.* ***117*** *1735.*

Price:

10 mg / $159.00 0
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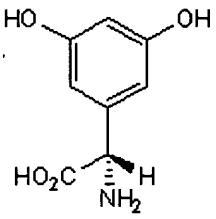
0805 (S)-3,5-DHPG



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Biological Activity:

Selective group I mGlu receptor agonist.

References:

Schoepp *et al (1994) 3,5-Dihydroxyphenylglycine is a highly selective agonist for phosphoinositide-linked metabotropic glutamate receptors in the rat hippocampus. J.Neurochem.* ***63*** *769.* ***Baker*** *et al (1995) Enzymatic resolution and pharmacological activity of the enantiomers of 3,5-dihydroxyphenylglycine, a metabotropic glutamate receptor agonist. Bioorg.Med.Chem.Lett.* ***5*** *223.* ***Sekiyama*** *et al (1996) Structure-activity relationships of new agonists and antagonists of different metabotropic glutamate receptor subtypes. Br.J.Pharmacol.* ***117*** *1493.* ***Wisniewski and Carr*** *(2002) (S)-3,5-DHPG: a review. CNS Drug Rev.* ***8*** *101.*

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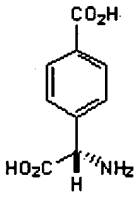
0323 (S)-4-Carboxyphenylglycine



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Biological Activity:

Competitive group I metabotropic glutamate receptor antagonist, with selectivity for $mGlu_{1a/1a}$ over $mGlu_{5a/5b}$.

References:

Birse *et al (1993) Phenylglycine derivatives as new pharmacological tools for investigating the role of metabotropic glutamate receptors in the central nervous system. Neuroscience* ***52*** *481.* ***Eaton*** *et al (1993) Competitive antagonism at metabotropic glutamate receptors by (S)-4-carboxyphenylglycine (CPG) and (RS)-α-methyl-4-carboxyphenylglycine (MCPG). Eur.J.Pharmacol.Mol.Pharmacol.Sect.* ***244*** *195.* ***Brabet*** *et al (1995) Phenylglycine derivatives discriminate between mGluR1- and mGluR5-mediated responses. Neuropharmacology* ***34*** *895.* ***Doherty*** *et al (1999) Antagonist activity of α-substituted 4-carboxyphenylglycine analogues at group I metabotropic glutamate receptors expressed in CHO cells. Br.J.Pharmacol.* ***126*** *205.*

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10 mg / $159.00 0

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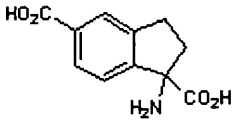

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Biological Activity:

A relatively potent and selective antagonist of group I metabotropic glutamate receptors ($mGlu_{1a}$), having no effect on group II ($mGlu_2$) or group III ($mGlu_4$) receptors expressed individually in baby hamster kidney cells. Has no effect on ionotropic glutamate receptors. Centrally active following systemic administration in vivo.

References:

Pellicciari *et al (1995) 1-Aminoindan-1,5-dicarboxylic acid: a novel antagonist at phospholipase C-linked metabotropic glutamate receptors. J.Med.Chem.**38** 3717.* ***Nielsen*** *et al (1997) Class I mGlu receptor antagonist 1-aminoindan-1,5-dicarboxylic acid blocks contextual but not cue conditioning in rats. Eur. J. Pharmacol. **326** 105.* ***Moroni*** *et al (1997) Pharmacological characterization of 1-aminoindan-1,5-dicarboxylic acid, a potent mGluR1 antagonist. J.Pharmacol.Exp.Ther. **281** 721*

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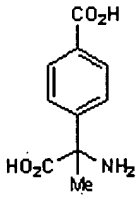
0336 (*RS*)-MCPG



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Biological Activity:

Non-selective group I/group II metabotropic glutamate receptor antagonist. See (S)-isomer (Cat. No. 0337).

References:

Eaton *et al (1993) Competitive antagonism at metabotropic glutamate receptors by (S)-4-carboxyphenylglycine (CPG) and (RS)-α-methyl-4-carboxyphenylglycine (MCPG). Eur.J.Pharmacol.Mol.Pharmacol.Sect.* ***244*** *195.* ***Collingridge and Watkins*** *(1994) Phenylglycine derivatives as metabotropic glutamate receptor antagonists. TiPS* ***15*** *333.* ***Joly*** *et al (1995) Molecular, functional and pharmacological characterization of the metabotropic glutamate receptor Type 5 splice variants: comparison with mGluR1. J.Neurosci.* ***15*** *3970.*

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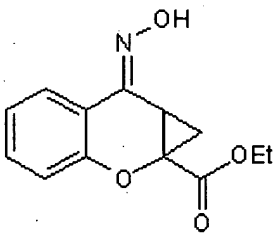
1028 CPCCOEt



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Biological Activity:

hmGlu$_1$ subtype selective non-competitive antagonist (IC_{50} = 6.5 μM). Has no agonist or antagonist activity at hmGlu$_{2, 4a, 5a, 7b, 8a}$ or ionotropic receptors at concentrations of up to 100 μM.

References:

Annoura *et al (1996) A novel class of antagonists for metabotropic glutamate receptors, 7-(hydroxyimino)cyclopropa[b] chromen-1a-carboxylates. Bioorg.Med.Chem.Lett.* ***6*** *763.* ***Hermans*** *et al (1998) Reversible and non-competitive antagonist profile of CPCCOEt at the human type 1α metabotropic glutamate receptor. Neuropharmacology* ***37*** *1645.* ***Litschig*** *et al (1999) CPCCOEt, a noncompetitive metabotropic glutamate receptor 1 antagonist, inhibits receptor signaling without affecting glutamate binding. Mol.Pharmacol.* ***55*** *453.*

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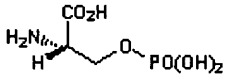
0238 *O*-Phospho-L-serine

Alternative name(s):

L-SOP



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Biological Activity:

Group III metabotropic glutamate receptor agonist; analogue of L-AP4 (Cat. No. 0103).

References:

Eriksen and Thomsen *(1995) [^{3}H]-L-2-amino-4-phosphonobutyrate labels a metabotropic glutamate receptor, mGluR4a. Br.J.Pharmacol.* ***116*** *3279.* ***Bruno*** *et al (1996) Activation of group III metabotropic glutamate receptors is neuroprotective in cortical cultures. Eur.J.Pharmacol.* ***310*** *61.* ***Thoreson and Ulphani*** *(1995) Pharmacology of selective and non-selective metabotropic glutamate receptor agonists at L-AP4 receptors in ON bipolar cells. Brain Res.* ***676*** *93.* ***Wright and Schoepp*** *(1996) Differentiation of group 2 and group 3 metabotropic glutamate receptor cAMP responses in the rat hippocampus. Eur.J.Pharmacol.* ***297*** *275.*

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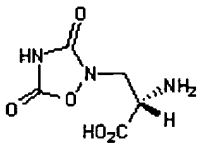
0188 L-Quisqualic acid



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Biological Activity:

Glutamate receptor agonist acting at AMPA receptors and metabotropic glutamate receptors positively linked to phosphoionositide hydrolysis. Sensitises neurons in hippocampus to depolarization by L-AP6 (the so called 'quis' effect).

References:

Porter *et al (1992) (S)-Homoquisqualate: a potent agonist at the glutamate metabotropic receptor. Br.J.Pharmacol.* ***106*** *509.* ***Schulte*** *et al (1994) Utilization of the resolved L-isomer of 2-amino-6-phosphohexanoic acid (L-AP6) as a selective agonist for a quisqualate-sensitized site in hippocampal CA1 pyramidal neurons. Brain Res.* ***649*** *203.* ***Littman*** *et al (1995) Effects of quisqualic acid analogs on metabotropic glutamate receptors coupled to phosphoinositide hydrolysis in rat hippocampus. Neuropharmacology* ***34*** *829.*

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10 mg / $155.00 0

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- MK-801, (+)-[3-^{3}H]-, 1mCi (37MBq)

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Product details

Radiochemical Purity is >97%

Ligands & Hormones, Radiolabeled

Receptor-related research has long been enabled by the continual availability of new radiolabeled ligands selected to keep pace with new discoveries. PerkinElmer offers a wide range of products and services for receptor research and drug discovery, including over 400 state-of-the-art radioligands. If you do not find exactly what you need, we invite you to take advantage of our custom labeling services, in which we will work with you, scientist to scientist, to prepare the custom radiolabeled ligand that meets your specifications.

CAS Number: [77086-22-7]
Specific Activity: 15-30Ci(555-1110GBq)/mmol
Concentration: 1mCi/mL

Radionuclide: ^{3}H
Molecular Formula: $C_{20}H_{19}NO_4$
Molecular Weight: 221.3

Storage and shipping

Storage Conditions: Store at -20°C
Shipping Conditions: Shipped in dry ice
Shipping Method: Air/Airborne, ground if local to Boston
Additional Information: This is a radioactive product - shipping address must have a licence to receive radioactive materials.

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